Complete Summary

GUIDELINE TITLE

Diagnosis and treatment of Wilson disease: an update.

BIBLIOGRAPHIC SOURCE(S)

Roberts EA, Schilsky ML, American Association for Study of Liver Diseases (AASLD). Diagnosis and treatment of Wilson disease: an update. Hepatology 2008 Jun;47(6):2089-111. [253 references] PubMed

GUIDELINE STATUS

This is the current release of the guideline.

This guideline updates a previous version: Roberts EA, Schilsky ML. A practice guideline on Wilson disease. Hepatology 2003 Jun;37(6):1475-92.

COMPLETE SUMMARY CONTENT

SCOPE
METHODOLOGY - including Rating Scheme and Cost Analysis
RECOMMENDATIONS
EVIDENCE SUPPORTING THE RECOMMENDATIONS
BENEFITS/HARMS OF IMPLEMENTING THE GUIDELINE RECOMMENDATIONS
CONTRAINDICATIONS
QUALIFYING STATEMENTS
IMPLEMENTATION OF THE GUIDELINE
INSTITUTE OF MEDICINE (IOM) NATIONAL HEALTHCARE QUALITY REPORT CATEGORIES
IDENTIFYING INFORMATION AND AVAILABILITY
DISCLAIMER

SCOPE

DISEASE/CONDITION(S)

Wilson disease (WD; hepatolenticular degeneration)

GUIDELINE CATEGORY

Diagnosis
Management
Screening
Treatment

CLINICAL SPECIALTY

Family Practice
Gastroenterology
Internal Medicine
Medical Genetics
Pediatrics

INTENDED USERS

Physicians

GUIDELINE OBJECTIVE(S)

To provide a data-supported approach to the diagnosis and treatment of patients with Wilsons disease

TARGET POPULATION

- Children and adults with suspected Wilson disease (e.g., with unexplained hepatic, neurological, or neuropsychiatric abnormalities)
- Children and adults diagnosed with Wilson disease
- First-degree relatives of patients diagnosed with Wilson disease (*screening*)

INTERVENTIONS AND PRACTICES CONSIDERED

Diagnosis/Screening

1. History and physical examination
2. Diagnostic testing
    - Complete blood count
    - Serum ceruloplasmin
    - Slit-lamp examination (Kayser-Fleischer rings)
    - Basal 24-hour urinary excretion of copper
    - Penicillamine challenge studies in children
    - Liver biopsy for hepatic parenchymal copper content
    - Neurologic evaluation and radiologic imaging of the brain by magnetic resonance imaging (MRI)
    - Mutation analysis by whole gene sequencing
    - Genetic screening of first-degree relatives based on haplotype analysis or specific testing for known mutations

Treatment

1. Chelating agent (D-penicillamine or trientine)
2. Diet (avoiding intake of foods and water with high copper concentrations)
3. Zinc
4. Liver transplantation
5. Treatment options considered but not specifically recommended:
    - Antioxidants (e.g., vitamin E)
    - Tetrathiomolybdate (not commercially available in the U.S.)

Management/Monitoring

1. Serum copper and ceruloplasmin
2. Liver biochemistries and international normalized ratio
3. Physical examination
4. Complete blood count with differential
5. Urinalysis for patients receiving chelators
6. Repeat Kayser-Fleischer ring examination for patients with questionable compliance
7. Yearly measurement of 24-hour urinary excretion of copper for patients on medication or more frequently if there are issues of compliance
8. Lifelong treatment unless a liver transplantation has been performed

MAJOR OUTCOMES CONSIDERED

- Side effects of pharmacologic treatment
- Effectiveness of treatment options (e.g., survival rates following liver transplantation, associated morbidity)

METHODOLOGY

METHODS USED TO COLLECT/SELECT EVIDENCE

Hand-searches of Published Literature (Primary Sources)
Searches of Electronic Databases

DESCRIPTION OF METHODS USED TO COLLECT/SELECT THE EVIDENCE

These guidelines are based on the following: (1) formal review and analysis of the recently-published literature on the topic including Medline search; (2) American College of Physicians Manual for Assessing Health Practices and Designing Practice Guidelines; (3) guideline policies, including the American Association for the Study of Liver Diseases (AASLD) Policy on the Development and Use of Practice Guidelines and the American Gastroenterological Association Policy Statement on Guidelines; (4) the experience of the authors in the specified topic.

NUMBER OF SOURCE DOCUMENTS

Not stated

METHODS USED TO ASSESS THE QUALITY AND STRENGTH OF THE EVIDENCE

Weighting According to a Rating Scheme (Scheme Given)

RATING SCHEME FOR THE STRENGTH OF THE EVIDENCE

Levels of Evidence

Level A Data derived from multiple randomized clinical trials or meta-analyses

Level B Data derived from a single randomized trial, or nonrandomized studies

Level C Only consensus opinion of experts, case studies, or standard-of-care

METHODS USED TO ANALYZE THE EVIDENCE

Systematic Review

DESCRIPTION OF THE METHODS USED TO ANALYZE THE EVIDENCE

Not stated

METHODS USED TO FORMULATE THE RECOMMENDATIONS

Expert Consensus

DESCRIPTION OF METHODS USED TO FORMULATE THE RECOMMENDATIONS

Not stated

RATING SCHEME FOR THE STRENGTH OF THE RECOMMENDATIONS

Grading System for Recommendations

Class I Conditions for which there is evidence and/or general agreement that a given procedure or treatment is beneficial, useful, and effective

Class II Conditions for which there is conflicting evidence and/or a divergence of opinion about the usefulness/efficacy of a procedure or treatment

Class IIa Weight of evidence/opinion is in favor of usefulness efficacy

Class IIb Usefulness efficacy is less well established by evidence/opinion

Class III Conditions for which there is evidence and/or general agreement that a procedure/treatment is not useful/effective and in some cases may be harmful

COST ANALYSIS

A formal cost analysis was not performed and published cost analyses were not reviewed.

METHOD OF GUIDELINE VALIDATION

Peer Review

DESCRIPTION OF METHOD OF GUIDELINE VALIDATION

This guideline has been approved by the American Association for the Study of Liver Diseases (AASLD) and represents the position of the association. The guideline was produced in collaboration with the Practice Guidelines Committee of the AASLD which provided extensive peer review of the manuscript.

RECOMMENDATIONS

MAJOR RECOMMENDATIONS

The grading system for the class of recommendations (I, II, IIa, IIb, III) and the levels of evidence (A–C) is defined at the end of the "Major Recommendations."

Clinical Features

1. Wilson Disease (WD) should be considered in any individual between the ages of 3 and 55 years with liver abnormalities of uncertain cause. Age alone should not be the basis for eliminating a diagnosis of WD (**Class I, Level B**).
2. WD must be excluded in any patient with unexplained liver disease along with neurological or neuropsychiatric disorder (**Class I, Level B**).
3. In a patient in whom WD is suspected, Kayser-Fleischer rings should be sought by slit-lamp examination by a skilled examiner. The absence of Kayser-Fleischer rings does not exclude the diagnosis of WD, even in patients with predominantly neurological disease (**Class I, Level B**).

Diagnostic Testing

Ceruloplasmin

4. An extremely low serum ceruloplasmin level (<50 mg/L or <5 mg/dL) should be taken as strong evidence for the diagnosis of WD. Modestly subnormal levels suggest further evaluation is necessary. Serum ceruloplasmin within the normal range does not exclude the diagnosis (**Class I, Level B**).

Urinary Copper Excretion

5. Basal 24-hour urinary excretion of copper should be obtained in all patients in whom the diagnosis of WD is being considered. The amount of copper excreted in the 24-hour period is typically >100 micrograms (1.6 micromols) in symptomatic patients, but finding >40 micrograms (>0.6 micromol or >600 nmol) may indicate WD and requires further investigation (**Class I, Level B**).
6. Penicillamine challenge studies may be performed for the purpose of obtaining further evidence for the diagnosis of WD in symptomatic children if basal urinary copper excretion is <100 micrograms/24 hours (1.6 micromols/24 hours). Values for the penicillamine challenge test of >1600 micrograms copper/24 hours (>25micromols/24 hours) following the administration of 500 mg of D-penicillamine at the beginning and again 12 hours later during the 24-hour urine collection are found in patients with WD. The predictive value of this test in adults is unknown (**Class I, Level B**).

Hepatic Parenchymal Copper Concentration

7. Hepatic parenchymal copper content >250 micrograms/g dry weight provides critical diagnostic information and should be obtained in cases where the diagnosis is not straightforward and in younger patients. In untreated patients, normal hepatic copper content (<40 to 50 micrograms/g dry weight) almost always excludes a diagnosis of WD. Further diagnostic testing is indicated for patients with intermediate copper concentrations (70 to 250 micrograms/g dry weight) especially if there is active liver disease or other symptoms of WD (**Class I, Level B**).

Neurological Evaluation and Radiologic Imaging of the Brain

8. Neurologic evaluation and radiologic imaging of the brain, preferably by magnetic resonance (MR) imaging, should be considered prior to treatment in all patients with neurologic WD and should be part of the evaluation of any patient presenting with neurological symptoms consistent with WD (**Class I, Level C**).

Genetic Studies

9. Mutation analysis by whole-gene sequencing is possible and should be performed on individuals in whom the diagnosis is difficult to establish by clinical and biochemical testing. Haplotype analysis or specific testing for known mutations can be used for family screening of first-degree relatives of patients with WD. A clinical geneticist may be required to interpret the results (**Class I, Level B**).

Diagnostic Considerations in Specific Target Populations

"Mimic" Liver Diseases and Acute Liver Failure

10. Patients in the pediatric age bracket who present a clinical picture of autoimmune hepatitis should be investigated for WD (**Class I, Level B**).
11. Adult patients with atypical autoimmune hepatitis or who respond poorly to standard corticosteroid therapy should also be investigated for WD (**Class I, Level C**).
12. WD should be considered in the differential diagnosis of patients presenting with nonalcoholic fatty liver disease or who have pathologic findings of nonalcoholic steatohepatitis (**Class IIb, Level C**).
13. WD should be suspected in any patient presenting with acute hepatic failure with Coombs-negative intravascular hemolysis, modest elevations in serum aminotransferases, or low serum alkaline phosphatase and ratio of alkaline phosphatase to bilirubin of <2 (**Class I, Level B**).

Family Screening

14. First-degree relatives of any patient newly diagnosed with WD must be screened for WD. (**Class I, Level A**).

Treatment

15. Initial treatment for symptomatic patients should include a chelating agent (D-penicillamine or trientine). Trientine may be better tolerated (**Class I, Level B**).
16. Patients should avoid intake of foods and water with high concentrations of copper, especially during the first year of treatment (**Class I, Level C**).
17. Treatment of presymptomatic patients or those on maintenance therapy can be accomplished with a chelating agent or with zinc. Trientine may be better tolerated (**Class I, Level B**).

Treatment in Specific Clinical Situations

18. Patients with acute liver failure due to WD should be referred for and treated with liver transplantation immediately (**Class I, Level B**).
19. Patients with decompensated cirrhosis unresponsive to chelation treatment should be evaluated promptly for liver transplantation (**Class I, Level B**).
20. Treatment for WD should be continued during pregnancy, but dosage reduction is advisable for D-penicillamine and trientine (**Class I, Level C**).
21. Treatment is lifelong and should not be discontinued, unless a liver transplant has been performed (**Class I, Level B**).

Treatment Targets and Monitoring of Treatment

22. For routine monitoring, serum copper and ceruloplasmin, liver biochemistries and international normalized ratio, complete blood count and urinalysis (especially for those on chelation therapy), and physical examination should be performed regularly, at least twice annually. Patients receiving chelation therapy require a complete blood count and urinalysis regularly, no matter how long they have been on treatment (**Class I, Level C**).
23. The 24-hour urinary excretion of copper while on medication should be measured yearly, or more frequently if there are questions on compliance or if dosage of medications is adjusted. The estimated serum non–ceruloplasmin bound copper may be elevated in situations of non-adherence and extremely low in situations of overtreatment (**Class I, Level C**).

Definitions:

Levels of Evidence

Level A Data derived from multiple randomized clinical trials or meta-analyses

Level B Data derived from a single randomized trial, or nonrandomized studies

Level C Only consensus opinion of experts, case studies, or standard-of-care

Grading System for Recommendations

Class I Conditions for which there is evidence and/or general agreement that a given procedure or treatment is beneficial, useful, and effective

Class II Conditions for which there is conflicting evidence and/or a divergence of opinion about the usefulness/efficacy of a procedure or treatment

Class IIa Weight of evidence/opinion is in favor of usefulness efficacy

Class IIb Usefulness efficacy is less well established by evidence/opinion

Class III Conditions for which there is evidence and/or general agreement that a procedure/treatment is not useful/effective and in some cases may be harmful

CLINICAL ALGORITHM(S)

Algorithms are provided in the original guideline document for the following:

- The approach to diagnosis of Wilson disease (WD) in a patient with unexplained liver disease
- The approach to the diagnosis of WD in a patient with a neurological disorder or psychiatric disease with or without liver disease
- Screening for WD in sibling or child of a patient with secure diagnosis of WD

EVIDENCE SUPPORTING THE RECOMMENDATIONS

TYPE OF EVIDENCE SUPPORTING THE RECOMMENDATIONS

The guidelines are based on review of the published literature and the personal experience of the authors. The type of supporting evidence is identified and graded for each recommendation.

BENEFITS/HARMS OF IMPLEMENTING THE GUIDELINE RECOMMENDATIONS

POTENTIAL BENEFITS

- Effective and timely diagnosis and treatment of persons with Wilson disease (WD)
- Improved compliance with treatment
- Reduction in treatment side effects
- Reduction in WD-associated morbidity

POTENTIAL HARMS

D-Penicillamine

- Worsening of neurologic symptoms has been reported in 10% to 50% of patients with Wilson disease (WD) treated with penicillamine during the initial phase of treatment.
- Severe side effects requiring the drug to be discontinued occur in approximately 30% of patients. Early sensitivity reactions marked by fever and cutaneous eruptions, lymphadenopathy, neutropenia or thrombocytopenia, and proteinuria may occur during the first 1 to 3 weeks.
- Late reactions include nephrotoxicity, usually heralded by proteinuria or the appearance of other cellular elements in the urine, for which discontinuation of D-penicillamine should be immediate. Other late reactions include a lupus-like syndrome marked by hematuria, proteinuria, positive antinuclear

antibody, and with higher dosages of D-penicillamine, no longer typically used for treating WD, Goodpasture's syndrome. Significant bone marrow toxicity includes severe thrombocytopenia or total aplasia. Dermatologic toxicities reported include progeric changes in the skin and elastosis perforans serpiginosa, and pemphigus or pemphigoid lesions, lichen planus, and aphthous stomatitis. Very late side effects include nephrotoxicity, severe allergic response upon restarting the drug after it has been discontinued, myasthenia gravis, polymyositis, loss of taste, immunoglobulin A depression, and serous retinitis. Hepatotoxicity has been reported. Hepatic siderosis has been reported in association with treated patients with reduced levels of serum ceruloplasmin and non-ceruloplasmin bound copper.

Trientine

- Neurological worsening after beginning treatment with trientine has been reported but appears much less common than with penicillamine.
- No hypersensitivity reactions have been reported with trientine, although a fixed cutaneous drug reaction was observed in one patient. Pancytopenia has rarely been reported. Trientine also chelates iron, and coadministration of trientine and iron should be avoided because the complex with iron is toxic. A reversible sideroblastic anemia may be a consequence of overtreatment and resultant copper deficiency. Lupus-like reactions have also been reported in some WD patients treated with trientine; however, these patients were almost all uniformly treated previously with penicillamine, so the true frequency of this reaction when trientine is used *de novo* is unknown.
- Use in patients with primary biliary cirrhosis revealed that trientine may cause hemorrhagic gastritis, loss of taste, and rashes. Recent evidence suggests that copper deficiency induced by trientine can result in iron overload in livers of patients with WD.

Zinc

- Gastric irritation is the main problem with zinc and may be dependent on the salt employed. Hepatic deterioration has been occasionally reported when zinc was commenced, fatal in one case. Also, zinc may have immunosuppressant effects and reduce leukocyte chemotaxis.
- Elevations in serum lipase and/or amylase may occur, without clinical or radiologic evidence of pancreatitis. Whether high-dose zinc is safe for patients with impaired renal function is not yet established.

CONTRAINDICATIONS

CONTRAINDICATIONS

Women taking D-penicillamine should not breast-feed because the drug is excreted into breast milk and might harm the infant. Little is known about the safety of trientine and zinc in breast milk.

QUALIFYING STATEMENTS

QUALIFYING STATEMENTS

- Intended for physicians, these recommendations suggest preferred approaches to the diagnostic, therapeutic, and preventive aspects of care. They are intended to be flexible, in contrast to standards of care, which are inflexible policies to be followed in every case.
- A significant problem with the literature on Wilson disease is that patients are sufficiently rare to preclude large cohort studies or randomized controlled trials; moreover, most treatment modalities were developed at a time when conventions for drug assessment were less stringent than at present.

IMPLEMENTATION OF THE GUIDELINE

DESCRIPTION OF IMPLEMENTATION STRATEGY

An implementation strategy was not provided.

IMPLEMENTATION TOOLS

Clinical Algorithm
Personal Digital Assistant (PDA) Downloads

For information about availability, see the "Availability of Companion Documents" and "Patient Resources" fields below.

INSTITUTE OF MEDICINE (IOM) NATIONAL HEALTHCARE QUALITY REPORT CATEGORIES

IOM CARE NEED

Getting Better
Living with Illness

IOM DOMAIN

Effectiveness

IDENTIFYING INFORMATION AND AVAILABILITY

BIBLIOGRAPHIC SOURCE(S)

Roberts EA, Schilsky ML, American Association for Study of Liver Diseases (AASLD). Diagnosis and treatment of Wilson disease: an update. Hepatology 2008 Jun;47(6):2089-111. [253 references] PubMed

ADAPTATION

Not applicable: The guideline was not adapted from another source.

DATE RELEASED

2003 Jun (revised 2008 Jun)

GUIDELINE DEVELOPER(S)

American Association for the Study of Liver Diseases - Private Nonprofit Research Organization

SOURCE(S) OF FUNDING

American Association for the Study of Liver Diseases

GUIDELINE COMMITTEE

Practice Guidelines Committee

COMPOSITION OF GROUP THAT AUTHORED THE GUIDELINE

Primary Authors: Eve A. Roberts; Michael L. Schilsky

Committee Members: Margaret C. Shuhart, MD, MS, (Committee Chair); Gary L. Davis, MD (Board Liaison); Kiran Bambha, MD; Andres Cardenas, MD, MMSc; Timothy J. Davern, MD; Christopher P. Day, MD, PhD; Steven-Huy B. Han, MD; Charles D. Howell, MD; Lawrence U. Liu, MD; Paul Martin, MD; Nancy Reau, MD; Bruce A. Runyon, MD; Jayant A. Talwalkar, MD, MPH; John B. Wong, MD; Colina Yim, RN, MN

FINANCIAL DISCLOSURES/CONFLICTS OF INTEREST

Potential conflict of interest: Nothing to report.

GUIDELINE STATUS

This is the current release of the guideline.

This guideline updates a previous version: Roberts EA, Schilsky ML. A practice guideline on Wilson disease. Hepatology 2003 Jun;37(6):1475-92.

GUIDELINE AVAILABILITY

Electronic copies: Available in Portable Document Format (PDF) from the American Association for the Study of Liver Diseases Web site.

Print copies: Available from the American Association for the Study of Liver Diseases, 1729 King Street, Suite 200; Alexandria, VA 22314; Phone: 703-299-9766; Web site: www.aasld.org; e-mail: aasld@aasld.org.

AVAILABILITY OF COMPANION DOCUMENTS

This guideline is available as a Personal Digital Assistant (PDA) download via the APPRISOR™ Document Viewer from www.apprisor.com.

PATIENT RESOURCES

None available

NGC STATUS

This NGC summary was completed by ECRI on February 17, 2004. The information was verified by the guideline developer on March 16, 2004. This NGC summary was updated by ECRI Institute on October 13, 2008. The updated information was verified by the guideline developer on November 24, 2008.

COPYRIGHT STATEMENT

DISCLAIMER

NGC DISCLAIMER

The National Guideline Clearinghouse™ (NGC) does not develop, produce, approve, or endorse the guidelines represented on this site.

All guidelines summarized by NGC and hosted on our site are produced under the auspices of medical specialty societies, relevant professional associations, public or private organizations, other government agencies, health care organizations or plans, and similar entities.

Guidelines represented on the NGC Web site are submitted by guideline developers, and are screened solely to determine that they meet the NGC Inclusion Criteria which may be found at http://www.guideline.gov/about/inclusion.aspx .

NGC, AHRQ, and its contractor ECRI Institute make no warranties concerning the content or clinical efficacy or effectiveness of the clinical practice guidelines and related materials represented on this site. Moreover, the views and opinions of developers or authors of guidelines represented on this site do not necessarily state or reflect those of NGC, AHRQ, or its contractor ECRI Institute, and inclusion or hosting of guidelines in NGC may not be used for advertising or commercial endorsement purposes.

Readers with questions regarding guideline content are directed to contact the guideline developer.

Date Modified: 12/15/2008


DEPARTMENT OF HEALTH & HUMAN SERVICES • USA